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Original

Relationship between Fatigue and Nocturnal Problems Related to Parkinson's Disease

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Summary

In patients with Parkinson's disease (PD), fatigue and sleep disturbances are important non-motor symptoms. In this study, we aimed to evaluate the relationship between fatigue and sleep disturbances in patients with Parkinson's disease (PD). A total of 93 outpatients with PD (age, 69.7 ± 8.9 years) and 93 healthy controls (age, 69.6 ± 10.2 years) were included in this study. The participants completed the Parkinson Fatigue Scale (PFS), Epworth Sleepiness Scale (ESS), Parkinson's disease sleep scale (PDSS)-2 and Beck Depression Inventory (BDI)-II. For PD patients, the PD Questionnaire (PDQ-39) was used to evaluate quality of life. Fatigue was defined as a PFS score of 3.3 or greater. Fatigue was observed in 7.5% of healthy controls and 44.0% of PD patients ($p < 0.001$). In the healthy control group, subjects with fatigue were older than those without fatigue, but there was no difference in the PDSS-2, ESS or BDI-II scores. PD patients with fatigue had significantly higher scores of the ESS, BDI-II, PDQ-39 and PDSS-2 and greater motor symptoms compared with those without fatigue. Fatigue was associated with the PDSS-2 sub-item 2 (Difficulty falling asleep), item 10 (Pain in arms or legs), item 13 (Tremor on waking), item 14 (Tired and sleepy after waking in the morning) and item 15 (Snoring or difficulties in breathing). Logistic regression analysis showed that the PDSS-2 subitem 14 (Tired and sleepy after waking in the morning) and the PDQ-39 summary index were significant determinants for fatigue. In conclusion, we showed the significant relationship between fatigue and various aspects of PD-related nocturnal problems. Our findings emphasize the importance of fatigue assessment in patients with PD.

Key Words: Parkinson's disease, sleep disturbances, fatigue, non-motor symptoms

Introduction

Parkinson's disease (PD) is a movement disorder characterized by resting tremor, rigidity, and bradykinesia due to degeneration of nigrostriatal dopaminergic neurons. Additionally, non-motor symptoms such as sleep disturbances, depression, cognitive impairment and fatigue, presumably not attributable to dopaminergic deficits, are common problems, affecting almost all patients with PD. Since non-motor symptoms can compromise quality of life (QOL) as equally as motor symptoms, screening and management are imperative. In a

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multicenter study consisting of 1,072 patients with PD, 98.6% reported the non-motor symptoms[1]. Among non-motor symptoms, fatigue, which is defined by a lack of energy, exhaustion and tiredness, is observed in approximately 50% of patients and is associated with severity of motor symptoms. Fatigue can precede the onset of motor symptoms and is associated with other non-motor symptoms such as depression, sleep disturbances and autonomic symptoms[2]. In early PD patients, fatigue was associated with sleep disturbances, anxiety and motor symptoms over time[3]. By contrast, patients with PD exhibit various nocturnal problems including sleep maintenance insomnia due to nocturnal motor and non-motor symptoms, rapid eye movement sleep behavior disorder (RBD), excessive daytime sleepiness (EDS), restless legs syndrome and sleep apnea syndrome. Also, disease-related pathology involving the brainstem and hypothalamus, which regulate the sleep-wake cycle and the effects of dopaminergic drug can contribute to sleep disturbances[4]. Various sleep disturbances including sleep maintenance insomnia, EDS and RLS have been reported to increase after PD onset [5-7]. In 227 newly diagnosed PD patients, sleep, fatigue, mood and attention have a significant impact on the patients' quality of life over a 2-year follow-up period[8]. In a previous study, a significant correlation between depressive symptoms and sleep disturbances was found, and daytime sleepiness, dystonia, tremor and sleep fragmentation were the most common nocturnal problems in depressed patients with PD[9]. A recent multicenter study from Japan including 1,020 patients showed fatigue and sleep disturbances in 77.0% and 73.7% of patients, respectively[10]. In a previous multicenter study performed in Japan showed that 43% of PD patients suffered from fatigue, and the determinants of fatigue were impaired QOL and sleep disturbances as measured by the PD sleep scale (PDSS)[11]. However, there has been little research on what types of nocturnal problems are involved in fatigue. In this study, we used the PDSS-2, a revised version of the PDSS, to examine the details of nocturnal symptoms related to fatigue.

Subjects and Methods

Subjects

Data from a single-center, cross-sectional, case-controlled study conducted at the Department of Neurology, Dokkyo Medical University Hospital[12] were analyzed to assess a relationship between fatigue and sleep disturbances. The study participants comprised of 93 consecutive outpatients with PD (69.7 ± 8.9 years; 50 men and 43 women) and 93 age- and gender-matched control subjects (69.6 ± 10.2 years; 47 men and 46 women). Control subjects with no history of neurological or psychiatric diseases were recruited from outpatient staff and their family members or friends. Clinical diagnosis of PD was made according to the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria[13]. Atypical parkinsonian syndrome, such as multiple system atrophy and progressive supranuclear palsy, and vascular parkinsonism were excluded by brain imaging and clinical examination. Drug-induced parkinsonism was excluded based on medication history. Patients with dementia based on the DSM-IV criteria[14], bedridden patients or patients who were not able to answer the questionnaire were excluded from this study.

Clinical assessment

Hoehn and Yahr (HY) staging was used to assess disease severity[15]. The Unified Parkinson's Disease Rating Scale (UPDRS) parts III and IV were used to evaluate motor symptoms and complications of treatment, respectively[16]. QOL of patients with PD was evaluated using the Parkinson's Disease Questionnaire (PDQ-39)[17]. The Beck Depression Inventory (BDI)-II was used to evaluate depressive symptoms[18], and the Japanese version of the PDSS-2 was used to evaluate nocturnal problems[12]. The PDSS-2 consists of 15 individual items for assessing nocturnal non-motor and motor problems (see appendix 1 for details). Daytime sleepiness was measured using the Japanese version of the Epworth Sleepiness Scale (ESS)[19]. The Parkinson Fatigue Scale (PFS) was used to assess PD-related fatigue[20]. The PFS consists of 16 symptoms related to fatigue, each of which is rated on a score of 1 (strongly disagree) to 5 (strongly agree). The overall PFS score is calculated as the average of all items. Fatigue was defined as a mean PFS score of 3.3 or greater, as previously defined[11,20]. RBD symptoms were assessed using the RBD screening questionnaire Japanese version (RBDSQ-J)[21]. Dopamine agonist dosage and the total levodopa

Table 1 Characteristics of patients with PD and controls

	PD	Controls	p value
N (M/F)	93 (50/43)	93 (47/46)	0.66
Age (yrs)	69.7 ± 8.9	69.6 ± 10.2	0.94
BMI (kg/m^2)	22.3 ± 2.8	22.9 ± 3.1	0.18
Fatigue, n (%)	41 (44.1)	7 (7.5)	**< 0.001**
RBDSQ-J	3.3 ± 2.5	1.7 ± 1.7	**< 0.001**
ESS	6.6 ± 4.5	4.7 ± 3.0	**< 0.001**
PDSS-2 total score	15.0 ± 9.7	9.1 ± 6.6	**< 0.001**
PDQ-39 summary index	29.1 ± 21.7	NA	
BDI-II	13.3 ± 9.3	8.5 ± 6.8	**< 0.001**
LED (mg/day)	385.1 ± 315.0	NA	

BMI = body mass index; RBDSQ-J = rapid eye movement sleep behavior disorder questionnaire Japanese version; ESS = Epworth Sleepiness Scale; PDSS-2 = Parkinson's disease sleep scale-2; PDQ-39 = Parkinson's disease questionnaire-39; BDI-II = Beck Depression Inventory-II; LED = levodopa equivalent dose

equivalent dose (LED) was calculated based on methods previously reported conversion factors[22]. This study was performed in accordance with the Declaration of Helsinki and was approved by the institutional review boards of Dokkyo Medical University. Written informed consent was given by all subjects enrolled in the study.

Statistical analysis

The Mann-Whitney U-test or an unpaired t-test was utilized when appropriate to compare continuous variables, and the Chi-Square or Fisher's exact test was performed to compare the differences in frequencies between the two groups. The correlations between the PFS with other clinical variables were analyzed using Spearman's rank correlation coefficients. Multiple logistic regression with a forward selection likelihood ratio was performed to determine the contributing factors to fatigue in PD patients, included variables with the p value < 0.1 in Table 2 except for age and sex. A two-tailed p value < 0.05 was considered to be statistically significant. The data analysis was performed using IBM SPSS Statistics software version 26.0 (IBM SPSS, Inc., Tokyo, Japan).

Results

Table 1 shows characteristics of patients and controls. Fatigue was more prevalent in PD patients compared to healthy subjects (44.0% vs 7.5%, p < 0.001). The RBDSQ-J, ESS, PDSS-2, and BDI-II scores were significantly higher in the patient group than in the control group. In the control group, individuals with fatigue were older that those without fatigue (77.3 ± 9.7 years vs. 68.9 ± 10.0 years, p = 0.041), but there was no difference in the PDSS-2, ESS or BDI-II scores. In the PD group, patients with fatigue had higher scores of the ESS, BDI-II, PDQ-39 summary index, PDSS-2 and UPDRS part III compared to those without fatigue (Table 2). As for the PDSS-2 subitems, patients with fatigue had higher scores on the PDSS-2 sub-item 2 (Difficulty falling asleep), item 10 (Pain in arms or legs), item 13 (Tremor on waking), item 14 (Tired and sleepy after waking in the morning) and item 15 (Snoring or difficulties in breathing), as compared with patients without fatigue. A correlation analysis between the PFS and clinical parameters showed that the PFS score was significantly positively correlated with age, HY stage and scores of the UPDRS III, PDSS-2 total, PDQ-39 summary index, and BDI-II (Table 3). Regarding the PDSS-2 subitems, the PFS was positively correlated with the items 8 (Get up at night to pass urine), 9 (Uncomfortable and immobility at night), 10 (Pain in arms or legs), 13 (Tremor on waking), 14 (Tired and sleepy after waking in the morning) and 15 (Snoring or difficulties in breathing). Logistic regression analysis showed the PDSS-2 subitem 14 (Tired and sleepy after waking in the morning) and the PDQ-39 summary index were significant determinants for fatigue (Table 4).

Table 2 Comparison of the clinical characteristics of PD patients with and without fatigue

	PD with fatigue	PD without fatigue	p value
N (M/F)	41 (24/17)	52 (26/26)	0.24
Age (yrs)	70.6 ± 10.1	68.8 ± 7.8	0.33
BMI (kg/m^2)	22.8 ± 2.7	22 ± 2.9	0.16
Disease duration (yrs)	6.3 ± 6.5	7.2 ± 5.9	0.48
HY stage	2.7 ± 0.8	2.6 ± 0.8	0.38
UPDRS III	27.0 ± 14.0	19.9 ± 13.1	**0.014**
UPDRS IV	1.9 ± 2.4	1.7 ± 2.3	0.66
LED (mg/day)	405.9 ± 275.1	368.4 ± 345.5	0.57
ESS	7.9 ± 5.0	5.5 ± 3.8	**0.013**
PDSS-2 total score	17.8 ± 9.7	12.7 ± 9.1	**0.011**
PDSS-2 sub-scores			
Item 1	1.0 ± 1.1	1.0 ± 1.4	0.91
Item 2	1.5 ± 1.3	0.8 ± 1.2	**0.019**
Item 3	2.2 ± 1.2	1.8 ± 1.3	0.18
Item 4	1.1 ± 1.3	1.0 ± 1.2	0.57
Item 5	0.8 ± 1.0	0.6 ± 1.0	0.57
Item 6	0.8 ± 1.1	0.6 ± 1.0	0.33
Item 7	0.4 ± 0.9	0.3 ± 0.6	0.38
Item 8	2.8 ± 1.3	2.4 ± 1.3	0.17
Item 9	1.1 ± 1.1	0.8 ± 1.1	0.16
Item 10	1.1 ± 1.1	0.5 ± 1.0	**0.0089**
Item 11	1.0 ± 1.1	0.6 ± 1.0	0.15
Item 12	0.7 ± 1.1	0.5 ± 1.0	0.22
Item 13	1.1 ± 1.2	0.6 ± 1.2	**0.043**
Item 14	1.3 ± 1.0	0.6 ± 0.9	**0.0012**
Item 15	0.8 ± 0.9	0.5 ± 0.8	**0.040**
PDQ-39 summary index	43.9 ± 19.6	16.9 ± 14.7	**< 0.0001**
BDI-II	18.8 ± 9.1	8.8 ± 6.8	**< 0.0001**
RBDSQ-J	3.6 ± 2.5	3.1 ± 2.6	0.31

Discussion

In our study, we showed that fatigue was closely related to impaired QOL, motor symptoms, daytime sleepiness, PD-related nocturnal problems and depressive symptoms. Also, the severity of fatigue was correlated with age, disease severity, motor symptoms, PD-related nocturnal problems, QOL and depressive symptoms. Similarly, Mantri et al[23] reported a significant correlation between fatigue, depressive symptoms, motor symptoms and worse QOL in PD patients with the association between fatigue and worse QOL being greater in patients with severe depressive symptoms. However, sleep disturbances were not assessed in their study. Huang et al[24] reported postural instability and gait disorder (PIGD) subtype had more severe nocturnal problems and fatigue compared with tremor dominant subtype. Of note, sleep disturbances and fatigue were the most relevant factors affecting QOL, independent of PIGD or tremor dominant subtypes. The PIGD subtype has been reported to have more severe motor symptoms and faster progression than tremor dominant subtype[25]. We also reported the ESS and PDSS-2 scores were higher in patients with PIGD subtype than tremor dominant subtype[26]. Although we failed to find an association between fatigue and the RBDSQ-J score, PD patients with severe fatigue had less amount of REM sleep with a higher percentage of REM sleep without atonia, the characteristic polysomnographic hallmark of RBD[27].

In our study, detailed analysis of the PDSS-2 subitems showed that fatigue was associated with difficulty falling asleep, pain in arms or legs, tremor on waking, tired and sleepy after waking in the morning,

and snoring or difficulties in breathing. The previous studies have shown associations between sleep disturbances and fatigue[11,12,24], but PD-related nocturnal problems have not been well characterized. In a 12 week double-blinded, placebo-controlled, pilot trial including 30 patients with PD rasagiline improved fatigue[28]. In a prospective study, higher levels of fatigue were associated with female, depressive symptoms, dependency in activities of daily living and better cognition, and lower levels of fatigue were associated with the use of dopamine agonists[29]. Therefore, appropriate treatment of nocturnal and early morning symptoms with dopamine agonists or non-dopaminergic agents may improve fatigue in patients with PD.

Table 3 Correlation coefficients between the PFS and other clinical parameters in patients with PD

	PD patients
Age	**.23***
BMI	.08
Disease duration	−.03
HY stage	**.21***
UPDRS III	**.36***
UPDRS IV	.15
ESS	**.33***
PDSS-2 total score	**.29****
PDSS-2 sub-items	
Item 1	.10
Item 2	.19
Item 3	.14
Item 4	.05
Item 5	.14
Item 6	.18
Item 7	.02
Item 8	**.21***
Item 9	**.21***
Item 10	**.25***
Item 11	.16
Item 12	.15
Item 13	**.28****
Item 14	**.33****
Item 15	**.25***
PDQ-39 summary index	**.72****
BDI-II	**.63****
RBDSQJ	.19

*$p < 0.05$, **$p < 0.01$. *Spearman's rank correlation.*

Fatigue could be normal physiologic reactions to intense activity. In healthy individuals, predictable, transient fatigue does not negatively affect daily life activities[30]. On the other hand, chronic, unpredictable, rest-unresponsive fatigue becomes clinically significant in patients with PD. PD-related fatigue is proposed as a sense of exhaustion unexplained by drug effects, other medical, or psychiatric disorders, and is associated with reduced motivation and nonrestorative rest, or constraints on activities[31]. Since we intended to investigate clinically relevant fatigue, we used the widely accepted cutoff for the PFS in this study. Although fatigue also can cause sleepiness, the relationship between EDS and fatigue is discussed[32,33]. In 90 patients with PD, excessive daytime fatigue was present in 42% of PD, but was not associated with EDS[34]. In our study the PFS and ESS scores were moderately correlated; however, in logistic regression analysis, the ESS was not a significant determinant of fatigue. In the logistic regression analysis of fatigue, the PDSS-2 subitem 14 remained, which was considered to be an overlapping item of fatigue and sleep disturbances.

Exact pathophysiological mechanisms of fatigue are unclear; however, abnormal basal ganglia- frontal loops, an imbalance between neurotransmitters such as dopamine and serotonin, an altered hypothalamus-pituitary-adrenal axis, neuroinflammation, and cardiac sympathetic denervation, have been suggested to be involved[35]. The clinical studies showed no differences in measure of striatal dopamine transporters between

Table 4 Logistic regression analysis of clinical variables predictive of fatigue (PFS ≥ 3.3) in PD patients

	OR (95% CI)	P
Item 14 (Tired and sleepy after waking in the morning)	1.759 (1.012-3.058)	**0.045**
PDQ 39 summary index	1.086 (1.049-1.124)	**< 0.0001**

Using forward selection likelihood ratio.
Independent variables; age, gender, UPDRS III, PDSS sub-items 2, 10, 13, 14 and 15, BDI-II, ESS and PDQ-39 summary index.

fatigue and non-fatigue group[36,37], but reduced serotonin transporter availability in the basal ganglia and limbic structures in PD patients with fatigue was reported[36].

Furthermore, a lower glucose metabolism in the right insular[38], right middle temporal gyrus and left middle occipital gyrus[39] has been linked to fatigue in patients with PD, suggesting that emotion, motivation and cognitive functions are implicated in PD-related fatigue.

A limitation of the study is that both fatigue and sleep were assessed by questionnaires and no other objective measures were available, although both scales have been widely used and validated. Second, the PD group and the control group may have had other comorbid diseases besides neurological or psychiatric diseases, which may have affected sleep and fatigue. Third, because this is a cross-sectional analysis and not a prospective study, the impact of disease progression on fatigue and sleep cannot be assessed.

In conclusion, our study results showed the significant relationship between fatigue and various aspects of PD-related nocturnal problems, highlighting the need for assessment of fatigue in patients with PD.

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Author contribution

Conception and design of the study, NN, HF, TS, HS and KS; acquisition and analysis of data: NN, HF, HS, KO, MS and KS; drafting the manuscript; NN and KS; review of the manuscript, HF, TS, HO and KS; supervision, KS.

Financial disclosure

Nothing to report.

Relevant conflicts of interest

None

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